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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/079,068	02/20/2002	Giorgio Trinchieri	WST85BUSA	7419

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EXAMINER	
SEHARASEYON, JEGATHEESAN	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/079,068	TRINCHIERI ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 5-12 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-11 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/29/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Receipt of Applicants' response filed 11/5/2004 to restriction/election of group V drawn to claim 24 without traverse is acknowledged. Applicants have amended claims 1 and 5-12 to depend on elected claim 24. Claims 2-4 and 13-23 are canceled as being drawn to non-elected subject matter. Applicants have added claims 25 and 26. Therefore, claims 5-11 and 24-26 will be considered as drawn to the elected group. In addition applicant has elected L-NMMA has the NO inhibitor. Thus, the restriction requirement is deemed proper and made FINAL.

Information Disclosure Statement

2. The PTO-1449 submitted on 4/29/2002 is acknowledged.

Drawings

3. The drawing submitted on 2/20/2002 is acknowledged.

Claim Objections

4. Claim 24 is objected to because of the following informalities: The nitric oxide on line 3 has been misspelled as nitric acid. Appropriate correction is required. The Office will assume that it is nitric oxide and proceed with the Office action.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 5-11 and 24-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 16 of U.S. Patent No. 6, 375, 944. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 16 of the allowed patent and claim 24 of the instant invention both describe composition comprising an effective amount of IL-12 and an effective amount of at least one agent selected from the group consisting of a nitric oxide inhibiting agent and a nitric oxide neutralizing agent.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time invention was made to generate therapeutic compositions comprising IL-12 and effective amounts nitric oxide inhibiting or nitric oxide neutralizing agents as described in the specification of U.S. Patent No. 6, 375, 944. The specification teaches the limitations of claims 5-11 and 24-26. Therefore the instant claims are obvious over claim 16 of U.S. Patent No. 6, 375, 944. Furthermore, the subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: The subject

matter of the instant invention is drawn to compositions comprising IL-12 and effective amounts nitric oxide inhibiting or nitric oxide neutralizing agents. These compounds are found in claim 16 of the of U. S. Patent No. 6, 375, 944. In addition, the limitations of dependent claims are recited in the specification of allowed patent. Of the original claims 39-41 from the parent application 09/395, 038 drawn to compositions claims 40 and 41 were rejoined with the method claims. Since these claims were grouped together in the restriction requirement the composition claims were not considered to be patentably distinct each from the other.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7a. Claims 5-11 and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scott et al. (U. S. Patent No. 5, 723, 127) in view of Orucevic et al. (1996) and Wahl et al. (U. S. Patent No. 5, 449, 688).

Scott et al. (U. S. Patent No. 5, 723, 127), supplied as reference (AC on IDS) teaches that the Interleukin-12 (IL-12) compositions are capable of eliciting the vaccinated host's cell-mediated immunity for a protective response to the pathogen (column 2, lines 35-40). The reference also teaches that the therapeutic compositions, comprising IL-12 to enhance the T-cell stimulation activity (column 3 lines 22-38). The reference also teaches both the IL-12 protein and DNA encoding the IL-12 (column 3, lines 5-10). Thus, addressing the limitations of the dependent claims 25 and 26.It is noted that the therapeutic effects of recombinant IL-12 (rIL-12) is often accompanied toxicity. Dose and schedule dependent toxicities have been seen during clinical trials (Atkins et al. AAU on IDS). Therefore, there is a compelling need to achieve low, non-toxic doses of Il-12 that provide adjuvanting effect. However, the reference does not teach the co-administration of an effective amount of nitric oxide inhibiting and/or neutralizing agent in a therapeutic composition with IL-12.

Orucevic et al. (1996) describe the inhibition of IL-2 induced NO production by inhibiting the synthesis of NO utilizing N-methyl-L-arginine (L-NMMA). It also describes that IL-2 in combination with L-NMMA was able to significantly reduce lung metastatic nodules (Fig. 7). L-NMMA is shown to prevent the toxic side effect of high doses of IL-2 when administered orally but not subcutaneously (p.44). They conclude that NO inhibitors, when scheduled properly and administered by the appropriate route to cause

NO inhibition *in vivo* without toxicity, can be valuable adjuncts to IL-2 therapy of cancer and infectious diseases (p. 45). Furthermore, it also describes that L-NMME also inhibits the synthesis of NO (p.44 and 45). Orucevic et al. reference also addresses the limitations present in the dependent claims 5-9.

Wahl et al. (U. S. Patent No. 5, 449, 688) describe nitric oxide scavengers such as hemoglobin or diethyldithiocarbamate (column 2, lines 25-29). It also teaches the use of NO scavengers to reduce inflammation (column 12, lines 15-24). Thus meeting the limitations of claims 10 and 11.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a composition comprising an effective amount of IL-12 as taught by Scott et al. and an effective amount of a nitric oxide inhibiting agent as described by Orucevic et al. and neutralizing agent as described Wahl et al. to generate a composition comprising IL-12 with **reduced toxicity** because Scott et al. teaches that therapeutic compositions containing IL-12 enhances the cell mediated immunity. One of ordinary skill in the art would have been motivated to use an effective amount of a nitric oxide inhibiting and neutralizing agents such as L-NMMA /L-NMME or hemoglobin to reduce the toxicity associated with IL-12 because nitric oxide inhibiting agent such L-NMMA are also **known** to inhibit the toxic side of high doses of IL-2 therapy in cancer patients (p.44). Furthermore, Wahl et al teach that hemoglobin inhibits nitric oxide. Therefore, the instant invention is *prima facie* obvious as a whole at the time it was made, over Scott et al. (U. S. Patent No. 5, 723, 127) in view of Orucevic et al. (1996) and Wahl et al. (U. S. Patent No. 5, 449, 688).

7. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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